Advanced Emergency Nursing Journal
Vol. 42, No. 4, pp. 243–253

APPLIED
PHARMACOLOGY

Column Editor: Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP

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Valproic Acid in the Treatment of Migraines

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ABSTRACT
Migraine headaches can be a disabling condition for patients. Fortunately, most patients can be successfully managed in the outpatient setting, however, there are a number of patients who may not respond to the abortive treatments that they have been prescribed. These patients often present to the emergency department (ED) for further assistance with the management of their condition. Migraines are the fourth most common cause of ED visits and are associated with an estimated annual cost of $17 billion in the United States. Familiarity with abortive treatments is critical for providers in the ED as are treatments, such as valproic acid, that may be considered in patients who do not respond to other treatment options. Many providers are more familiar with the role of valproic acid in the treatment of mood and seizure disorders, but its tolerability and the successes reported in the primary literature make it a reasonable consideration for patients with migraine who fail to respond to other therapies. This article briefly summarizes the therapies considered first line for abortive treatment in the setting of migraines and provides an overview of the primary literature describing the use of valproic acid in these patients. **Key words:** headache, migraines, treatment, valproic acid

MIGRAINES ARE a common disorder that are oftentimes managed on an outpatient basis. In some cases, the outpatient treatment regimen fails, and these patients may present to the emergency department (ED). In fact, migraine headache accounts for at least 1.2 million visits to the ED each year, and annual estimated costs are $700 million for ED visits and $375 million for inpatient hospitalizations (Insinga, Ng-Mak, & Hanson, 2011). The classic signs and symptoms described by patients include a disabling headache that may or may not be accompanied by light and/or sound sensitivity and nausea. Given that these patients commonly present to the ED, it is imperative that the health care team be familiar with the different treatment options that may be used in the acute management of migraines including those that are not as well known as valproic acid. This article provides a review of migraine headaches as well as

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Disclosure: *The authors report no conflicts of interest.*

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DOI: 10.1097/TME.0000000000000319

pharmacotherapy options for initial abortive treatment. An overview of valproic acid, dosing, and a literature review describing the role of this agent in the treatment of migraines is also provided.

MIGRAINE OVERVIEW

Epidemiology, Clinical Presentation, and Pathophysiology

Migraines are a neurological disorder that affect approximately 12% of the population. Both children and adults can suffer from this disorder, and the signs and symptoms can range from minor to severely debilitating. Migraines have been found to be more common in those who are 18–44 years of age and among women. About 18% of women experience migraines compared with 6% of men (Lipton, Stewart, Diamond, Diamond, & Reed, 2001).

A migraine is defined as a chronic headache that can last from 4 hr to days (Gilmore & Magdalena, 2011). Migraines are categorized into three phases: prodrome, aura, and headache. Some patients may experience a postdrome phase; however, this is not defined in the International Classification of Headache Disorders (Giffin, Lipton, Silberstein, Olesen, & Goadsby, 2016). The prodrome generally begins anywhere from a few hours to days prior to the onset of headache symptoms. Symptoms of prodrome may vary from patient to patient and generally include changes in mood, fatigue, insomnia, nausea, and constipation or diarrhea. The next phase is the aura, but not all patients will experience this phase. Aura occurs in about 30% of patients and occurs 20–60 min prior to the onset of a migraine (Gilmore & Magdalena, 2011; Goadsby, 2012). Symptoms of aura are neurological in nature and may consist of visual, sensory, or motor deficits. The headache phase of a migraine can be unilateral and pulsating and can range in duration from several hours to 72 hr. Pain severity varies from patient to patient and can range from mild to severe. Patients who present with a chief complaint of a migraine generally have unilateral pulsating pain that is associated with nausea and vomiting and/or sensitivity to light and sounds. Some patients may experience triggers that cause their migraines. Triggers can be food (e.g., alcohol, chocolate, processed meats), overstimulating environments (glaring or flickering lights, loud noises, and strong smells), and lifestyle factors (sleep excess or deficiency, depression, menstruation, stress, and strenuous physical activity).

The pathophysiology of migraines was originally thought to be due to the "vascular hypothesis" proposed by Willis and Wolff (Giffin et al., 2016). The theory stated that during a migraine the pain was caused because of the dilation of the cranial vessels. The more accepted mechanism is the neurovascular theory. Trigeminal nerve activation causes a release of calcitonin gene-related peptide, which is a known vasodilator; however, the mechanism of migraine and the associated pain is not well understood (Goadsby, Edvinsson, & Ekman, 1990; Goadsby, Lipton, & Ferrari, 2002). The pain may occur due to a combination of an altered perception and the activation of a neurovascular dilator mechanism that is specific for the first division of the trigeminal nerve (Goadsby et al., 2002; May, Buchel, Turner, & Goadsby, 2001).

Medications Commonly Used in the Treatment of Migraines

Both preventive and abortive treatments may be used in the management of migraines. Preventive therapy is intended to reduce the frequency of attacks, the severity of attacks, and migraine duration when and if they occur. It can also be used to help improve function and reduce disability in patients. This type of therapy is outside the scope of this review article, as it is primarily prescribed and implemented in the outpatient setting. Abortive treatment is used when a patient is currently experiencing a migraine. The goals of abortive treatment are rapid and consistent relief from headache, restored ability to function, minimal need for re-dosing, and minimal to no adverse effects (Goadsby et al., 2002).

Intravenous fluids should be considered in patients who present to the ED with signs and symptoms suggestive of migraine, as dehydration can be a trigger and nausea and vomiting may exacerbate the patient's migraine. There is limited strong evidence to support the administration of intravenous fluids, but other potential benefits include relief in malaise and prevention of some of the adverse effects associated with common abortive treatments (Gilmore & Magdalena, 2011).

Abortive therapies are most effective when given as soon as possible after the onset of signs and symptoms. Large single doses of the different agents that may be used are more efficacious than small repetitive doses. If the patient presents with nausea and vomiting, oral agents may be of little benefit. Pharmacological agents most commonly used as abortive therapies are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiemetics/dopamine receptor blockers. The triptans and dihydroergotamine are used in patients who are in more severe pain and do not respond to the previously mentioned therapies (Silberstein, 2000).

Medications that may be provided in the ED as abortive treatments include ketorolac 30 mg intravenously or 60 mg intramuscularly, metoclopramide 10 mg intravenously or prochlorperazine 10 mg intravenously, sumatriptan 6 mg subcutaneously, and dihydroergotamine 1 mg intravenously. Diphenhydramine 12.5–25 mg intravenously may be given in conjunction with the antiemetics/dopamine receptor blockers to prevent dystonic reactions (Kelley & Tepper, 2012a, 2012b). It is not uncommon for many of these medications to be given in combination as what is commonly known as a "migraine cocktail." Despite guidelines that recommend nonopioid medications as first-line therapy for severe migraine, opioids may be ordered for treatment of these patients. Given the high abuse potential of the opioids, it is recommended that they be used sparingly and in the setting of refractory migraine (Mayans & Walling, 2018).

Acetaminophen and NSAIDs are recommended as first-line treatments in mild to moderate migraine attacks. Of the two therapies, acetaminophen has been found to be less effective but does not result in gastric irritation or antiplatelet effects (Mayans & Walling, 2018). Based on the patient's ability to tolerate oral medications, ketorolac 30 mg intravenously or 60 mg intramuscularly can be considered and is reported to have a success rate of 60% (Kelly, 2000). Doses of 15 mg intravenously or 30 mg intramuscularly have been reported to have similar efficacy. Unfortunately, the primary literature is lacking in head-to-head trials comparing the NSAIDs, so availability and tolerability tend to be the deciding factor in agent selection (Mayans & Walling, 2018).

The triptans are considered a specific treatment of migraines, given their mechanism of action (i.e., inhibition of the release of vasoactive peptides, vasoconstriction, and blocking pain pathways in the brainstem) and are often an effective first-line treatment strategy for those patients presenting with a moderate or severe migraine. These medications may also activate serotonin 5-hydroxytryptamine (5-HT) 1b/1d receptors, which inhibit dural nociception (Tfelt-Hansen, De Vries, & Saxena, 2000). An important pearl for providers to keep in mind is that patients will respond differently to certain triptans (i.e., treatment failure to one triptan does not mean another triptan will also fail). A meta-analysis of seven triptans demonstrated that standard doses resulted in headache relief at 2 hr in 42%–76% of patients and complete pain relief in 18%–50% of patients at 2 hr. Sumatriptan is the most extensively studied triptan and can be given intranasally, orally, or as a subcutaneous injection. When administered subcutaneously, adverse events such as injection site reaction, chest heaviness, dizziness, malaise, and paresthesias may occur (Tfelt-Hansen, 1998). The 6-mg subcutaneous dose can be repeated in an hour if needed and has the most favorable number needed to treat for complete pain resolution at 2 hr (Mayans & Walling, 2018). Contraindications

to the triptans include a history of ischemic heart disease and uncontrolled hypertension. It is also important to keep in mind that triptans should not be used within 24 hr of the use of ergotamine preparations and that combination with monoamine oxidase inhibitors is contraindicated.

Dihydroergotamine is an α-adrenergic blocker and a potent 5-HT 1b/1d receptor agonist. This medication is available for intravenous, intramuscular, and subcutaneous use. When administered intravenously, it is often combined with an antiemetic (Colman et al., 2005). Similar to the triptans, dihydroergotamine is contraindicated in patients with hypertension or ischemic heart disease.

In the event that the aforementioned treatments have not resulted in migraine cessation or contraindications exist, intravenous valproic acid may be considered as another therapeutic option.

VALPROIC ACID

Mechanism of Action

Valproic acid increases the availability of γ-aminobutyric acid (GABA), resulting in an inhibitory effect. It can work by enhancing the action of GABA or mimic its inhibitory action on the postsynaptic receptor sites or block the voltage-dependent sodium channels and prevent the high-frequency repetitive neuronal firing. These mechanisms in conjunction with its ability to reduce serotonergic cell activity provide the rationale for the role of valproic acid in the treatment of migraines. More common indications for valproic acid include, but are not limited to, seizures and an array of mood disorders. Oral valproic acid has been studied and approved for the prophylaxis of migraine.

Primary Literature Review

Its use in migraine prophylaxis has sparked interest in the utility of intravenous valproic acid in the abortive treatment of acute migraine attacks. A review of the literature for the safety and efficacy of intravenous valproic acid in the management of acute migraine attack was conducted and is summarized within Table 1. The search was conducted using PubMed with the following search terms: valproic acid, migraine, and treatment. Overall, the primary literature is contradictory as there have been studies demonstrating headache relief 30 min postinfusion, similar relief to that of dihydroergotamine plus metoclopramide after 4 hr, and better pain reduction from prochlorperazine than that from valproic acid. Safety benefits from valproic acid to consider when comparing it with other agents include lack of cardiovascular side effects, lack of drug–drug interactions with the triptans and ergotamine preparations, lack of sedation, and the absence of potential for addiction or habituation.

In addition to the primary literature noted in Table 1, there were case reports about two patients experiencing a severe migraine with aura published in 2000. One of the patients was a 34-year-old woman who had a complicated migraine history and took oral carbamazepine 200 mg twice daily for migraine prophylaxis and routinely used oral or subcutaneous sumatriptan for migraine attacks. Prior to presentation and over the course of the previous several days, the patient had tried ergotamine/caffeine, sumatriptan, and prochlorperazine with no relief. As for the exact time frame of the dose of sumatriptan, it was not noted in the case report. Upon presentation, her migraine had been ongoing for more than 3 days and had resulted in her vomiting and becoming dehydrated. She received fluids, dihydroergotamine, meperidine, and prochlorperazine and experienced no relief of symptoms. Given her lack of response, the patient was treated with two doses of intravenous valproate 1,000 mg given over 1 hr each. Following this, the patient had complete resolution within 3 hr after the initiation of valproic acid. The second patient was a 28-year-old woman who experienced migraines two to four times monthly and was not prescribed prophylactic medications. She presented with a severe migraine that persisted for 2 days in

Table 1. Valproic acid for treatment of migraines literature review

Study citation	Study design	Valproic acid regimens studied alone or compared to others	Summary of results	Pertinent statistical results	Adverse events
Hering & Steiner, 1994	Open-label trial ($N = 24$)	Intravenous valproic acid 500 mg ± a second dose of valproic acid 500 mg at 1 hr	Cessation of migraine was reported by more than 50% of patients after 2 hr of administration	58% (95% CI [42, 72])	No significant adverse effects; a high incidence of gastrointestinal discomfort
Matthew, Kailasam, Meadors, Chernyzchev, & Gentry, 2000	Open-label trial ($N = 61$)	Intravenous valproic acid 300 mg	Headache severity on the Visual Analog Scale was significantly decreased in the valproate arm from 7.7 to 2.1 after treatment with valproic acid	$p \leq 0.001$	No serious adverse events were reported; two patients reported mild transient lightheadedness
Edwards, Norton, & Behnke, 2001	Open-label randomization ($N = 40$)	500 mg of intravenous valproic acid or 10 mg intramuscular metoclopramide + 1 mg of dihydroergotamine	50% of intravenous valproic acid; patients reported improvement from severe to mild/none at 1 hr vs. 55% in the metoclopramide + dihydroergotamine arm 60% vs. 50% reported improvement at 2 hr, 60% vs. 60% at 4 hr, and 60% vs. 90% at 24 hr Similar relief provided for both arms in regard to nausea, photophobia, and phonophobia	$p = 0.3635$	No patients in the valproic acid arm reported drug-related side effects; 15% of patients in the dihydroergotamine arm reported nausea and diarrhea within 4 hr

(*continues*)

Table 1. Valproic acid for treatment of migraines literature review (*Continued*)

Study citation	Study design	Valproic acid regimens studied alone or compared to others	Summary of results	Pertinent statistical results	Adverse events
Tanen, Miller, French, & Riffenburgh, 2003	Randomized, double-blind trial ($N = 40$)	500 mg of intravenous valproic acid over 2 min or 10 mg of intravenous prochlorperazine over 2 min	At 60 min, there was pain reduction; Visual Analog Scale score at 1 hr was greater for the prochlorperazine arm vs. the valproic acid arm (−64.5 vs. −9.0). 79% of patients in the valproic acid arm required rescue treatment vs. 25% of patients in the prochlorperazine arm	$p < 0.001$	No significant adverse effects were reported
Shahien, Saleh, & Bowirrat, 2011	Prospective open-label study ($N = 36$)	900–1,200 mg of intravenous valproic acid ± a second dose of 1,200 mg intravenous valproic acid within 20 min 89% of subjects received at least one medication prior to valproic acid; 36% of subjects received another medication after valproic acid	At 60 min, more than 75% of the patients had a reduction in pain from moderate/severe to mild/pain-free on a 10-point Visual Analog Scale	95% CI [1.32, 38.95]	No serious adverse events were reported; decreased nausea, disability, and photophobia were reported

(*continues*)

Table 1. Valproic acid for treatment of migraines literature review (*Continued*)

Study citation	Study design	Valproic acid regimens studied alone or compared to others	Summary of results	Pertinent statistical results	Adverse events
Friedman et al., 2014	Double-blind comparative trial (N = 330)	1,000 mg of valproic acid or 10 mg of metoclopramide or 30 mg of ketorolac intravenously over 15 min	Migraine pain relief at 1 hr: intravenous valproic acid arm improvement by a mean of 2.8 vs. 4.7 metoclopramide vs. 3.9 ketorolac Required rescue medication: 69% in the intravenous valproic acid arm vs. 33% in the metoclopramide arm vs. 52% in the ketorolac arm Sustained headache freedom: 4% in the intravenous valproic acid arm vs. 11% in the intravenous metoclopramide arm vs. 16% in the ketorolac arm	95% CI [2.3, 3.3]; 95% CI [4.2, 5.2]; 95% CI [3.3, 4.5]	No adverse events reported; 5% of patients in the metoclopramide group reported restlessness
Rahimdel, Mellat, Zeinali, Jafari, & Ayatollahi, 2014	Double-blind randomized clinical trial (N = 142)	400 mg of valproic acid in 200 ml of normal saline over 20 min + 2 ml of subcutaneous normal saline or 6 mg of sumatriptan subcutaneously + 200 ml of normal saline for 20 min	Pain decrement was reported at 30, 60, and 120 min in both groups ($p < 0.001$); however, no significant difference was reported between the groups	$p > 0.05$	Fewer patients among the valproic acid arm reported nausea and vomiting, face paresthesias, and hypotension; 37 of 45 patients in the valproic acid arm had no side effects, whereas 14 of 45 patients in the sumatriptan arm had no side effects ($p < 0.001$)

Note. CI = confidence interval.

conjunction with nausea and vomiting. The patient self-medicated with a combination of acetaminophen, isometheptene, dichloralphenazone, and sumatriptan without success. The patient was treated in the hospital with prochlorperazine and meperidine and had no improvement. Following these interventions, the provider ordered intravenous valproate 1,000 mg over 1 hr, followed by a repeat dose 4 hr later. Within 2 hours after the first dose, the patient reported improvement in her symptoms. All of these data led to the development of a few randomized controlled clinical trials that look at the efficacy of intravenous valproic acid compared with other standards of therapy (Norton, 2000).

Minimal data for intravenous valproic acid exist for its use in pediatric patients, but two pertinent retrospective chart reviews are included for review here. Authors of a 2005 retrospective review included all children who received intravenous valproic acid during an 18-month study period. Data related to the intensity of headache pain, time when relief was attained, pain-reduction scores, dose and durations of valproic acid infusions, pulse, blood pressure, respiratory rate, pulse oximetry, and adverse events were collected. Of the 31 children included, 58 required clinic visits and 71 received valproate infusions. Of the children in the study, 87.9% received intravenous dexamethasone and/or ondansetron to help with symptoms of nausea and vomiting associated with either migraine or administration of valproic acid. Most of the visits (77.6%) only required one dose of valproic acid, with a dose of 976 ± 85 mg infused over 12 ± 4 min for adequate pain relief. Those who required a second dose received a 500-mg fixed dose infused over 14 ± 6 min. Following the administration of the single infusion of valproic acid, the authors reported a 39.8% pain reduction with a time to maximum relief of 63 ± 31 min. There were no appreciable changes in vital signs or adverse events reported. Overall, the valproic acid infusions were well tolerated and helped relieve pain (Reither, Nickisch, & Merritt, 2005).

A retrospective chart review from 2009 to 2012 was conducted to assess the use of continuous intravenous valproate as an abortive therapy for pediatric migraines after initial abortive treatment. During the study period, 83 patients received a 20-mg/kg loading dose, followed by a continuous infusion of 1 mg/kg/hr. The continuous infusion was continued until maximal relief, based on clinical judgment, or a constant tolerable pain level according to the patient was achieved. At this point, patients were converted to the oral extended release formulation, with the dose being the same as what was administered over the previous 24 hr. Serum valproate levels were drawn at 4 and 24 hr after the loading dose was administered, and the infusion rate was adjusted to maintain serum levels between 80 and 100 mcg/ml. Twenty-four-hour serum levels were within goal range 91.9% of the time. Pain was assessed with age-appropriate scales. Per the results, 55 patients (66.2%) reported an excellent response (100% pain reduction), four (4.8%) a moderate response (50%–100% pain reduction), and 24 (28.9%) a poor response (less than 50% pain reduction). The continuous infusion resulted in minimal adverse effects as nausea occurred in 8.4% of patients and vomiting in 2.4% of patients (Zafar, Stewart, Toupin, Cook, & Baumann, 2018).

Initial Valproic Acid Regimens for Abortive Migraine Therapy

Because there are limited data on the appropriate dosing of valproic acid intravenously in the setting of acute migraine treatment, administration will vary on the basis of the prescribed regimen. Based on the data presented previously, valproic acid 500–1,000 mg intravenously may be prescribed with a repeat dose of 500 mg if migraine pain relief is not achieved. This regimen may be given at a rate of 50 mg/min. In the event that a loading dose (20 mg/kg) is ordered, it can be safely infused over 30–60 min. Following the administration of the loading dose, a continuous infusion of

1 mg/kg/hr may follow. It is important to note that the target serum concentration is 80–100 mcg/ml, so 4- and 24-hr levels should be obtained following administration of the loading dose.

Adverse Effects and Drug Interactions

The most common adverse effects of intravenous valproic acid provided throughout studies related to migraine dosing include nausea, vomiting, and diarrhea. These side effects could be related to the illness or the medication being administered. With lower doses or decreased infusion rates, it appears that adverse events among patients are diminished. Secondary to the major congenital malformations such as neural tube defects that are associated with valproic acid, it is not recommended for use in pregnant women and/or women of childbearing age (Voinescu & Pennel, 2015). Valproic acid carries a boxed warning concerning for hepatotoxicity; however, this is more of a concern in patients who are taking valproic acid in the long term as opposed to those who may receive it as an acute therapy. Incidents related to hepatotoxicity most commonly occur during the first 6 months of treatment and are often associated with nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting (Siemes et al., 1993).

Before administering valproic acid, health care team members should review the patient's profile for potentially severe drug–drug interactions. Although there are many drug–drug interactions associated with valproic acid, the most notable medications to screen for are other anticonvulsants, antidepressants, antibiotics (e.g., carbapenems), and warfarin. Valproic acid is heavily protein bound and inhibits key cytochrome P450 enzymes, so interactions with other common anticonvulsants (e.g., lamotrigine, phenytoin) should be noted and the patient monitored accordingly (Levy & Koch, 1982). As for warfarin, the patient's international normalized ratio should be monitored carefully to reduce the patient's risk of bleeding (Yoon, Giraldo, & Wijdicks, 2011).

CONCLUSION

Even though valproic acid is not considered a standard abortive therapy in the treatment of acute migraine headaches, it is important for providers to be familiar with its mechanism and the dosing strategies that have been studied in patients with migraine as it has been associated with some success. Based on the information available, it is a potential treatment option for those patients who do not respond to the more standard abortive therapies (i.e., NSAIDs, dopamine receptor blockers, triptans) or those who have contraindications to those same therapies. In order for intravenous valproic acid to have a more predominant role in the treatment of acute migraines, larger, randomized controlled trials with a standard dose need to be completed. Furthermore, intravenous valproic acid should be compared with more of the standard parenteral therapies administered in the ED when patients present after other agents have failed. These standard therapies include ketorolac, the dopamine receptor blockers, subcutaneous sumatriptan, and possibly dihydroergotamine.

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Disclosure Statement

The authors and planners have disclosed that they have no financial relationships related to this article.